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(54) **A method for the production of 6,12-dihydro-6-hydroxy-cannabidiol and the use thereof for the production of transdelta-9-tetrahydrocannabinol.**

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FR-A- 2 537 136
US-A- 4 116 979
US-A- 4 758 597

JOURNAL OF PHARMACEUTICAL SCIENCES. vol. 67, no. 1, January 1978, WASHINGTON US pages 27 - 32; E.R. GARRETT ET AL.: 'Stability of tetrahydrocannabinols II'

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Description

Cannabinoid compounds are components which can be isolated from Cannabis spp. Due to its physiological activity trans-delta-9-tetrahydrocannabinol (Δ^9-THC) is of substantial significance. This compound is also referred to as 6a,7,8,10a-tetradydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol.

The psychotropic but non-habit forming effects mean that this compound is of interest as pharmaceutical component.

The prior art discloses several different methods for the preparation of Δ^9-THC.

FR-A-25 37 136 discloses a process for the preparation of dibenzo[b,d]pyran derivatives using resorcinol and substituted cyclohexenal or cyclohexadiene compounds. US patent no. 4 116 979 teaches the preparation of trans-delta^9-tetrahydrocannabinol by reacting a substituted resorcinol with (+)-p-mentha-2,8-dien-1-ol. The preparation of a cannabinol derivative named carenadoil from resorcinol and car-4-en-3-ol is disclosed in US patent no. 4 758 597.

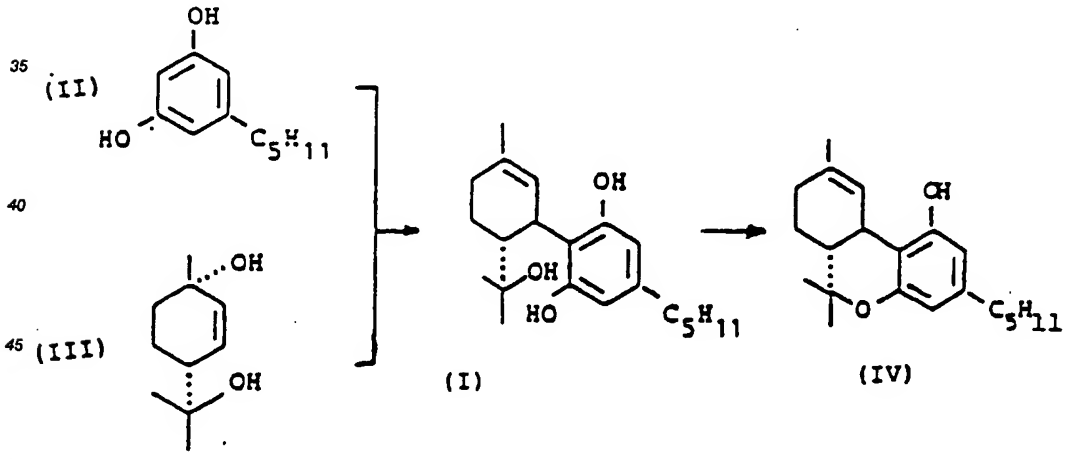
In conventional methods there is however the disadvantage that known synthesis paths lead to a number of by-products, which are very difficult to separate from the desired final product. Furthermore the final product is obtained in the form of a resinous mass, something that is hardly conducive to simple purification. Due to these disadvantages production on an industrial scale meets with substantial difficulties.

The compound 6,12-dihydro-6-hydroxy-cannabidiol described in the present application has so far not been either synthetically produced or used as an intermediate for the production of trans-delta-9-tetrahydrocannabinol. One reference to it in the literature (see Garrett et al., J. Pharm. Sci. 67 (1978) pages 27 - 32) only relates to the analytical chromatographic trace detection of one of a number of many other products of decomposition of delta-9-THC in an acidic solution. The compound has therefore not been produced in preparative quantities nor used for any sort of reactions. Furthermore the physical data of the compound have not been described previous to the present application.

One object of the present invention is therefore to provide a method for the production of trans-delta-9-tetrahydrocannabinol both with a sufficient purity and also on an industrial scale.

In order to achieve this object, firstly 6,12-dihydro-6-hydroxy-cannabidiol is produced as a crude intermediate, which may be readily purified by crystallization. This intermediate is then converted by ring condensation to the desired delta-9-THC.

The method of production in accordance with the invention will be made clear by the following reaction scheme:



In accordance with the invention the first step is to produce the intermediate 6,12-dihydro-6-hydroxy-cannabidiol which may also be termed 1,3-dihydroxy-2-[6-(1-hydroxy-1-methyl-ethyl)-3-methyl-2 -cyclohexene-1-yl]-5-pentyl-benzene. This compound is denoted I in the above scheme.

For the synthesis of 6,12-dihydro-6-hydroxy-cannabidiol as the intermediate in accordance with the invention the starting materials are the readily available olivetol (formula II) and cis-p-menth-2-ene-1,8-diol (formula III). The reaction is performed in a suitable solvent, aromatic hydrocarbons such as benzene and toluene, halogenated hydrocarbons such as methylene chloride, chloroform, dichloroethane and trich-

loroethane, ethers such as diethylether, diisopropylether and tetrahydrofuran having proved to be suitable. Furthermore it is possible to use mixtures of the said solvents.

Toluene, benzene, methylene chloride and chloroform are the preferred solvents for use in the method of the invention.

Preferably the reaction in accordance with the invention is performed in the presence of a suitable catalyst, proton acids such as for instance haloid acids, sulfuric acid, phosphoric acid, perchloric acid, organic sulfonic acids, such as for instance methanesulfonic acid and p-toluenesulfonic acid, carboxylic acids, such as for instance oxalic acid, trifluoroacetic acid and other Lewis acids, such for instance boron trifluoride, ferric chloride, zinc chloride, zinc bromide, stannic chloride, titanium chloride or iodine having proved to be suitable. Furthermore mixtures of the individual catalysts may be used in certain cases.

Preferably hydrochloric acid and p-toluenesulfonic acid are used in accordance with the invention.

The method may be performed at temperatures between approximately -30° C and +50° C, temperatures between 0° C and 20° C being preferred.

The reaction times are dependent on the solvent, the catalyst used and the reaction temperature. In fact it is possible to use reaction times between a few minutes and several hours.

The intermediate product produced may then be readily further purified by recrystallization. In this respect the use of petroleum ether has turned out to be suitable for the recrystallization.

Ring condensation may be used to produce the trans-delta-9-tetrahydrocannabinol (Δ^9-THC) from 6,12-dihydro-6-hydroxy-cannabidol. This reaction is performed in a suitable solvent with the use of suitable catalysts and water binding substances. The solvent is in the form of a hydrocarbon, as for instance hexane, heptane, cyclohexane, petroleum ether, aromatic hydrocarbons, such as for instance benzene, toluene, chorinated hydrocarbons, such as for instance methylene chloride, chloroform and dichloroethane. Preferably methylene chloride and chloroform are used. Furthermore mixtures of the solvents may be used.

As a catalyst for the ring condensation Lewis acids such as for instance zinc chloride, zinc bromide, boron trifluoride, ferric chloride, stannic chloride, titanium chloride or iodine are used, zinc chloride and zinc bromide having proved to be more particularly suitable.

Water binding substances such as neutral substances as for instance magnesium sulfate, sodium sulfate, calcium sulfate or molecular sieves may be used, the last-named having proved more particularly suitable.

The reaction is performed at a temperature between approximately -20° C and the boiling point of the corresponding solvent.

The reaction times are dependent on the catalyst, the solvent, the water binding substance and the reaction temperature. Dependent on the selected conditions times from a few minutes to several days are required.

For the man in the art it will be clear that the reactions in accordance with the invention may be also performed using such functionalized derivatives as may also be used for the synthesis of Δ^9 THC.

It is an advantage in the method in accordance with the invention that starting with readily available materials the intermediate product in the form of 6,12-dihydro-6-hydroxy-cannabidiol may be produced simply with a good yield and that such product may be purified without any great difficulty.

Starting with the intermediate product in accordance with the invention it is possible to obtain highly pure, that is to say low-isomer Δ^9 THC, the purification of the THC so obtained being possible by simple elution of a silica gel column. With the aid of the method described above it is possible to achieve a high, reproducible yield of the Δ^9 THC and the production of the final product is also possible on an industrial scale.

Example 1

The production of 6,12-dihydro-6-hydroxy-cannabidiol.

90 g of olivetol were agitated with 85g of cis-p-menth-2-ene-1,8,-diol and 4g of p-toluenesulfonic acid•H_2O in 4 1 methylene chloride for 24 hours at 20° C. Then extraction was performed once with 200 ml. of 4% calcium carbonate solution and the organic phase was reduced in vacuum to an oil. In this respect approximately 170 g of residue were obtained, which were dissolved in 1 l of petroleum ether (50/70) and extracted three times with respectively 300 ml of 0.5 N sodium hydroxide.

The petroleum ether phase was then run into a silica gel column (approximately 500 g of silica gel) and eluted with a mixture of petroleum ether (50/70) and diisopropylether (2:1). The eluate was reduced in volume under vacuum and the residue (approximately 102 g) was recrystallized from 600 ml of petroleum ether (50/70). 77 g of the desired product were obtained. This corresponds with a yield of about 46%. The

characteristic data of the 6,12-dihydro-6-hydroxy-cannabidiol were as follows:

Fusion point: 77 to 77.5 ° C.

Optical rotation: $[\alpha]_D^{20}$ = -70.3 ° C (c = 1.00; $CHCl_3$)

UV spectrum: (UV)λ_{max} (ethanol 95%) 275 nm (ϵ 1024)

λ_{max} (ethanol 95%) 281 nm (ϵ 987)

Infrared spectrum: (IR, KBr pellet) $[cm]^{-1}$ 3392, 2956, 2930, 2859, 1630, 1582, 1446, 1379, 1369, 1335, 1308, 1231, 1202, 1186, 1158, 1076, 1046, 1028.

Mass spectrum: (MS 70 eV, EI) m/z 332(M^+, 10), 314(29), 299(37), 297(10), 286(12), 271(44), 258(13), 246(11), 243(13), 231(100), 193(25), 174(12), 137(14), 93(18), 59(25), 43(63); TMS derivative: m/z 548 (M^+).

Nuclear magnetic resonance: (^{1}H-NMR, 60 MHz, $CDCl_3$) δ (ppm) 0.88 (tr, 3H, CH_3-18), 1.25 (s, 6H, CH_3-12), 1.30 (m, 4H, CH_2-17, CH_2-16), 1.57 (m, 2H, CH_2-15), 1.70 (m, 1H, CH-7α), 1.80 (s, 3H, CH_3-11), 1.90 (m, 1H, CH-6a), 1.97 (m, 1H, CH-7β), 2.09 (m, 2H, CH_2-8), 2.44 (dd, 2H, CH_2-14), 3.85 (m, l1H, CH-10a), 5.66 (m, 1H, CH-10), 6.37 (s, 2H, arom. H).

Capillary gas chromatography: (KGC, J & W DB5-15N, 60 to 250 ° C, 5 °/min. + 30 min. isotherm.; relative retention time [RRT]).

n-Hexadecane	RRT 1.000
Sample A of 6,12-dihydro-6-hydroxy-cannabidiol	RRT 2.121
Sample B of 6,12-dihydro-6-hydroxy-cannabidiol (TMS derivative)	RRT 1.946

Example 2

Production of trans-delta-9-tetrahydrocannabinol.

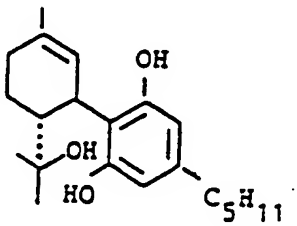
10 g of 6,12-dihydro-6-hydroxy-cannabidiol were dissolved in 300 ml of methylene chloride and held for 24 hours under reflux in the presence of 20 g of zinc bromide and 15 g of molecular sieve 3Å . Then filtration was performed and the filtrate reduced in volume. The residue was teen up in 100 ml of petroleum ether and run into a silica gel column (approximately 100 g of the gel). Then elution was performed with petroleum ether and the eluate was reduced in volume. The residue obtained was Δ^9-THC with a purity of ≥ 96%. In the cyclisation step a yield of about 72% could be obtained.

For both steps as shown in examples 1 and 2 respectively a total yield of about 33% (0.46 x 0.72) could be obtained, which is much higher than the yield of the known processes.

Claims

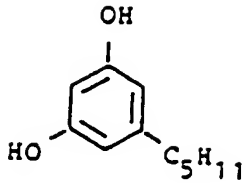
1. A method for the production of 6,12-dihydro-6-hydroxy-cannabidiol of the following formula:

(I)



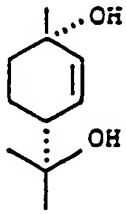
wherein olivetol with the following formula

(II)



is reacted with cis-p-menth-2-ene-1,8,-diol of the formula

(III)



in a solvent with the use of a catalyst and the product of the reaction is further purified by crystallization if necessary.

2. The method as claimed in claim 1, characterized in that the solvent is selected from the group consisting of aromatic hydrocarbons, halogenated hydrocarbons, ethers or mixtures thereof.

3. The method as claimed in claim 2, characterized in that the solvent is selected from the group consisting of toluene, benzene, methylene chloride and chloroform or mixtures thereof.

4. The method as claimed in any one of the preceding claims, characterized in that as a catalyst a proton acid, an organic sulfonic acid or another Lewis acid is used.

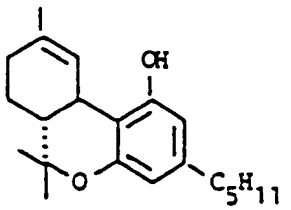
5. The method as claimed in claim 4, characterized in that as a catalyst hydrochloric acid or p-toluenesulfonic acid is used.

6. The method as claimed in any one of the preceding claims, characterized in that the 6,12-dihydro-6-hydroxy-cannabidiol is further purified by crystallization from petroleum ether.

7. 6,12-Dihydro-6-hydroxy-cannabidiol.

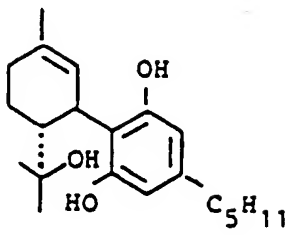
8. A method for the production of trans-delta-9-tetrahydrocannabinol of the formula:

(IV)



wherein 6,12-dihydro-6-hydroxy-cannabidiol which is obtainable by a method in accordance with any one of the claims 1 through 7, of the formula:

(I)



is subjected to a ring condensation.

9. The method as claimed in claim 8, characterized in that the ring condensation is performed in a solvent selected from the group consisting of hydrocarbons, aromatic hydrocarbons and chlorinated hydrocarbons.

10. The method as claimed in claim 9, characterized in that said solvent used is selected from the group consisting of methylene chloride and chloroform.

11. The method as claimed in any one of the preceding claims 8 through 10, characterized in that the ring condensation is performed in the presence of a Lewis acid as a catalyst.

12. The method as claimed in claim 11, characterized in that a catalyst selected from the group consisting of zinc chloride and zinc bromide is used.

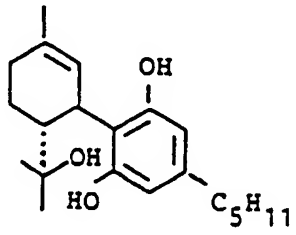
13. The method as claimed in any one of the preceding claims 8 through 12, characterized in that the ring condensation is performed in the presence of a water binding substance.

14. The method as claimed in claim 13, characterized in that the water binding substance is a molecular sieve.

Patentansprüche

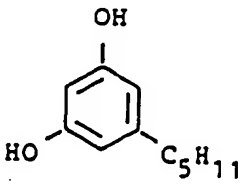
1. Verfahren zur Herstellung von 6,12-Dihydro-6-hydroxy-cannabidiol der folgenden Formel

(I)



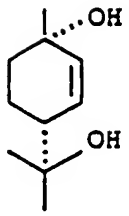
worin Olivetol mit folgender Formel

(II)



mit cis-p-Menth-2-en-1,8-diol der Formel

(III)



in einem Lösungmittel unter Verwendung eines Katalysators umgesetzt wird und das Reaktionsprodukt gegebenenfalls durch Kristallisation weiter gereinigt wird.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß das Lösungsmittel ausgewählt ist aus der Gruppe bestehend aus aromatischen Kohlenwasserstoffen, halogenierten Kohlenwasserstoffen, Ethern oder Mischungen davon.

3. Verfahren nach Anspruch 2, dadurch gekennzeichnet, daß das Lösungsmittel ausgewählt ist aus der Gruppe bestehend aus Toluol, Benzol, Methylenchlorid und Chloroform oder Mischungen davon.

4. Verfahren nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß als Katalysator eine Protonensäure, eine organische Sulfonsäure oder eine andere Lewissäure verwendet wird.

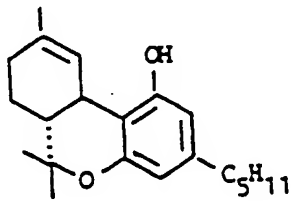
5. Verfahren nach Anspruch 4, dadurch gekennzeichnet, daß als Katalysator Salzsäure oder p-Toluolsulfonsäure verwendet wird.

6. Verfahren nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß das 6,12-Dihydro-6-hydroxy-cannabidiol durch Kristallisation aus Petrolether weiter gereinigt wird.

7. 6,12-Dihydro-6-hydroxy-cannabidiol.

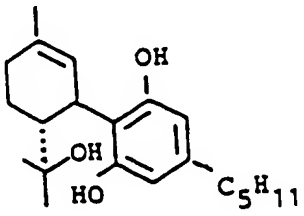
8. Verfahren zur Herstellung von Trans-delta-9-tetrahydrocannabinol der Formel

(IV)



worin 6,12-Dihydro-6-hydroxy-cannabidiol, das nach einem Verfahren gemäß einem der Ansprüche 1 bis 7 herstellbar ist, der Formel

(I)



einer Ringkondensation unterzogen wird.

9. Verfahren nach Anspruch 8, dadurch gekennzeichnet, daß die Ringkondensation in einem Lösungsmittel ausgewählt aus der Gruppe bestehend aus Kohlenwasserstoffen, aromatischen Kohlenwasserstoffen oder chlorierten Kohlenwasserstoffen durchgeführt wird.

10. Verfahren nach Anspruch 9, dadurch gekennzeichnet, daß besagtes verwendetes Lösungsmittel aus der Gruppe bestehend aus Methylenchlorid und Chloroform ausgewählt ist.

11. Verfahren nach einem der Ansprüche 8 bis 10, dadurch gekennzeichnet, daß die Ringkondensation in Gegenwart einer Lewissäure als Katalysator durchgeführt wird.

12. Verfahren nach Anspruch 11, dadurch gekennzeichnet, daß ein Katalysator ausgewählt aus der Gruppe bestehend aus Zinkchlorid und Zinkbromid verwendet wird.

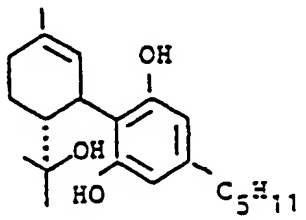
13. Verfahren nach einem der Ansprüche 8 bis 12, dadurch gekennzeichnet, daß die Ringkondensation in Gegenwart eines wasserbindenden Mittels durchgeführt wird.

14. Verfahren nach Anspruch 13, dadurch gekennzeichnet, daß das wasserbindende Mittel ein Molekularsieb ist.

Revendications

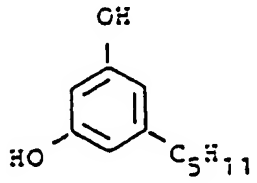
1. Procédé de production de 6,12-dihydro-6-hydroxy-cannabidiol répondant à la formule suivante :

(I)



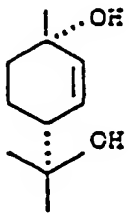
dans lequel de l'olivétol répondant à la formule suivante

(II)



est amené à réagir avec le cis-p-menth-2-ène-1,8-diol de formule

(III)



dans un solvant au moyen d'un catalyseur, et le produit de la réaction est soumis en outre, si nécessaire, à une purification par cristallisation.

2. Procédé suivant la revendication 1, caractérisé en ce que le solvant est choisi dans le groupe consistant en hydrocarbures aromatiques, hydrocarbures halogénés, éthers et leurs mélanges.

3. Procédé suivant la revendication 2, caractérisé en ce que le solvant est choisi dans le groupe consistant en toluène, benzène, chlorure de méthylène, chloroforme et leurs mélanges.

4. Procédé suivant l'une quelconque des revendications précédentes, caractérisé en ce que, comme catalyseur, un acide protonique, un acide sulfonique organique ou un autre acide de Lewis est utilisé.

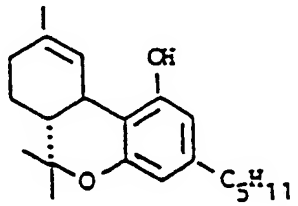
5. Procédé suivant la revendication 4, caractérisé en ce que, comme catalyseur, l'acide chlorhydrique ou l'acide p-toluènesulfonique est utilisé.

6. Procédé suivant l'une quelconque des revendications précédentes, caractérisé en ce que le 6,12-dihydro-6-hydroxy-cannabidiol est soumis en outre à une purification par cristallisation dans l'éther de pétrole.

7. 6,12-dihydro-6-hydroxy-cannabidiol

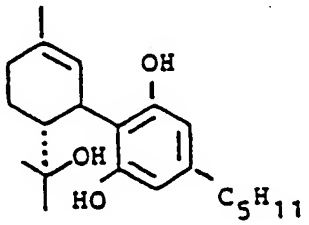
8. Procédé de production de trans-delta-9-tétrahydrocannabinol de formule :

(IV)



dans laquelle du 6,12-dihydro-6-hydroxy-cannabidiol qui peut être obtenu par un procédé suivant l'une quelconque des revendications 1 à 7 répondant à la formule :

(I)



est soumis à une cyclisation.

9. Procédé suivant la revendication 8, caractérisé en ce que la cyclisation est effectuée dans un solvant choisi dans le groupe consistant en hydrocarbures, hydrocarbures aromatiques et hydrocarbures chlorés.

10. Procédé suivant la revendication 9, caractérisé en ce que le solvant utilisé est choisi dans le groupe consistant en chlorure de méthylène et chloroforme.

11. Procédé suivant l'une quelconque des revendications 8 à 10 précédentes, caractérisé en ce que la cyclisation est effectuée en présence d'un acide de Lewis servant de catalyseur.

12. Procédé suivant la revendication 11, caractérisé en ce qu'un catalyseur choisi dans le groupe consistant en chlorure de zinc et bromure de zinc est utilise.

13. Procédé suivant l'une quelconque des revendications 8 à 12 précédentes, caractérisé en ce que la cyclisation est effectuée en présence d'une substance fixant l'eau.

14. Procédé suivant la revendication 13, caractérisé en ce que la substance fixant l'eau est un tamis moléculaire.